RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

ZrO_2-β-cyclodextrin catalyzed synthesis of 2,4,5-trisubstituted imidazoles and 1,2-disubstituted benzimidazoles under solvent free conditions and evaluation of their antibacterial study

Yarabhally R.Girish,[a] Kothanahally S. Sharath Kumar,[a] Kuntebommanahalli N. Thimmaiah,[b] Kanchugarakoppal S. Rangappa,[a*] and Sheena Shashikanth,[a*]

[a]*Department of Studies in Chemistry, Manasagangotri, University of Mysore, Mysore-570006.*

[b]*Department of Chemistry, Northwest Mississippi Community College/University of Mississippi, DeSoto Center, Southaven, Mississippi-38671, USA.*

*Corresponding author.

Tel. No.: +91-821-2419668
E-mail: shashis1956@gmail.com

Abstract

A series of 2,4,5-trisubstituted imidazoles and 1,2-disubstituted benzimidazoles catalyzed by ZrO_2-supported-β-cyclodextrin (ZrO_2-β-CD) under solvent free conditions have been synthesized and characterized by spectral methods. The nanoparticles (ZrO_2-β-CD), prepared by a simple one-pot-coprecipitation method and were characterized by PXRD, SEM, and TEM techniques. The nano (ZrO_2-β-CD) particles were found to be an effective heterogeneous reusable catalyst for the effective synthesis of imidazoles and benzimidazoles under solvent free conditions and all of the synthesized derivatives were evaluated for their antibacterial activity against six bacterial strains.

Keywords: Imidazoles, Benzimidazoles, Condensation, Regioselective, ZrO_2 supported -β-cyclodextrin nanoparticles (ZrO_2-β-CD).

Introduction

Imidazoles, an important class of five membered nitrogen containing heterocycles, play a vital role in the synthesis of biologically active molecules. These compounds are known to possess diverse biological applications as inhibitors of transforming growth factor-β type I receptor (ALK5), mGAT3 selective GABA uptake inhibitors, anti-inflammatory agents, anti-cancer agents, fungicides, antithrombotic agents, anti-alzheimer's agents, and for the determination of propyl gallate in edible oil.[1] These compounds also play an important role as parent π-conjugated backbone for organic chromophores for intramolecular charge-transfer process,[2] for enhanced charge transfer for hetero-junction solar cell applications,[3] and as a new building block for blue light emitting materials.[4] Imidazole-based heterocycles have also been used for energetic materials.[5] In addition phosphino imidazoles and imidazolium salts have been used for the synthesis of Suzuki C–C coupling reactions.[6]

Benzimidazole derivatives have drawn considerable attention due to their widespread biological applications such as antitumor,[7] antimicrobial,[8] anti-inflammatory,[9] antihelminthic[10] activities. In addition, benzimidazoles are important intermediates in various organic reactions.[11-13] Therefore, the synthesis of benzimidazoles has gained much importance in recent years. Several synthetic efforts have been made for the synthesis of benzimidazoles using various catalysts.[14-21]

The conventional methods for the synthesis of 2,4,5- trisubstituted imidazoles are mainly based on the cyclo condensation of a 1,2-diketone with an aldehyde using ammonium acetate as the nitrogen source.[22] Various catalysts under different reaction conditions have been employed for the synthesis of imidazole based derivatives.[23] Most of the reported methods suffer from one or the other serious drawbacks such as high reaction temperature, long duration, use of toxic and expensive chemicals as starting materials, use of moisture-sensitive catalysts and formation of

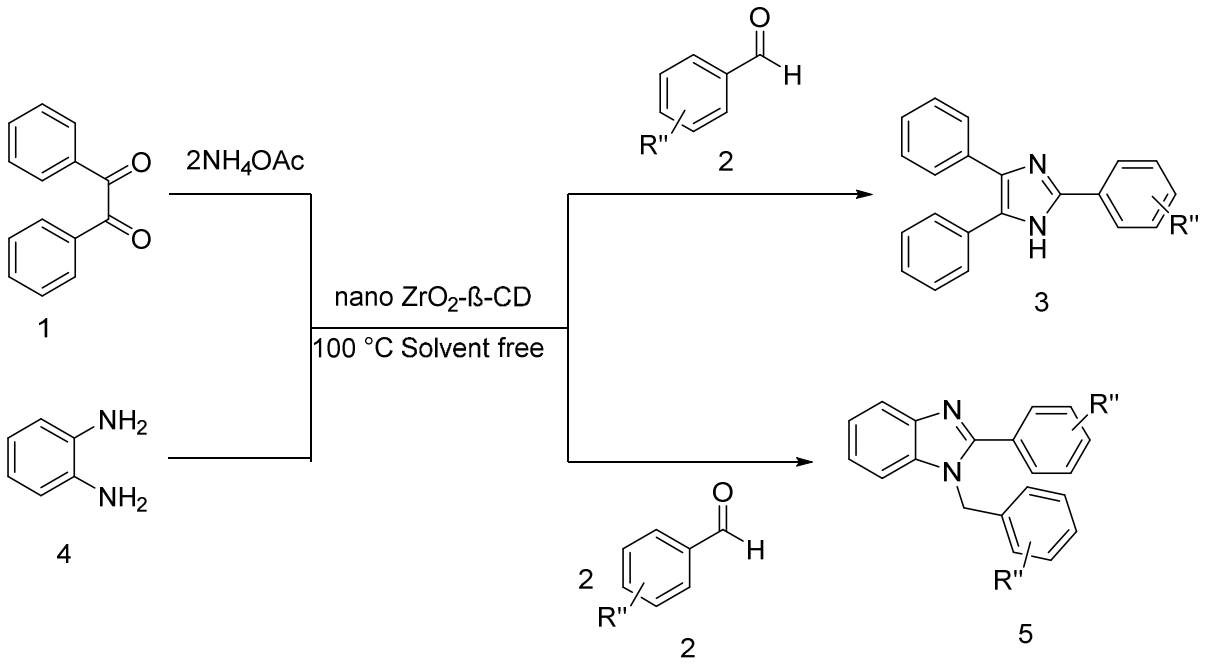
byproducts. Recently Nanoparticles have been extensively used in the field of medicinal chemistry,[24,25] heterocyclic chemistry,[26,27] as sensors for detection of hydrazine,[28] optoelectronic materials,[29] in enhancing the up-conversion luminescence,[30] and as electron transfer mediators in a bio-electrochemical systems.[31,32]

Cyclodextrins (CDs) are natural oligosaccharides linked by α-1,4-glycosidic linkage, having hydrophobic cavities inside and hydrophilic outside. The substrates can be entrapped in the hydrophobic cavity of the cyclodextrin felicitating the catalysis of the chemical reactions for higher selectivity. β-cyclodextrins have been extensively used in various biochemical applications such as for drug and gene delivery,[33] to detect micromolar quantities of Pb^{2+} in aqueous solution,[34] for removing diazepam from blood,[35] for optical sensing and chiroselective sensing of different substrates using a fluorescence resonance energy transfer (FRET).[36] In addition, β-cyclodextrin has also been used as catalyst for the synthesis of various hetrocycles.[37]

In recent years ZrO_2 nanoparticles have gained much attention in catalysis due to their specific amphoteric properties, excellent mechanical strength and stiffness, high thermal stability and dielectric properties.[38-40] ZrO_2 can exist in three polymorphic forms depending on the temperature range namely monoclinic (room temperature–1172 °C), tetragonal (1172–2347 °C) and cubic (above 2347 °C).[41,42] ZrO_2 have found wide spread applications in the field of science and technology.[43-54]

In continuation of our efforts in nanoparticles catalyzed synthesis of diverse nitrogen containing heterocycles,[55] we have described ZrO_2-β-CD catalyzed synthesis of imidazoles and 1,2-disubstituted benzimidazoles from readily available benzyl, 1,2-phenylenediamine, aldehydes and ammonium acetate under solvent free conditions (Scheme 1) using ZrO_2-β-CD as an

environment friendly and reusable heterogeneous catalyst (Scheme 1). It is note-worthy to mention that, ZrO_2-supported β-cyclodextrin nanoparticles have never been used in the field of synthetic organic chemistry for the synthesis of any heterocycles.



Scheme 1 Synthesis of 2,4,5-trisubstituted imidazoles by multi-component reaction of benzil, aldehydes, NH_4OAc, and synthesis of 1,2-disubstituted benzimidazoles using 1,2-diamine and aldehyde in the presence of ZrO_2 supported -β-cyclodextrin catalyst under solvent-free conditions.

Results and Discussion

The ZrO_2 nanoparticles-supported β-cyclodextrin nanoparticles (ZrO_2-β-CD) was prepared by a simple one-pot co-precipitation method by using $ZrOCl_2.8H_2O$, and NH_4OH (Scheme 2).[56] The morphology of the prepared ZrO_2-β-CD nanoparticles were characterized by ATR-IR, PXRD, SEM, TEM and EDAX analysis, which confirmed the successful preparation of the ZrO_2 -supported β-cyclodextrin nanoparticles.

Fig. 1 shows the ATR-IR spectrum of ZrO_2 -β-cyclodextrin nanoparticles. The bands observed at 844 and 510 cm^{-1}, which is due to asymmetric and symmetric stretching modes of ZrO_2. The broad band appears at 3337 cm^{-1} is for hydroxyl stretching vibration of β-cyclodextrin. The peak at 1348 corresponds to C-C stretching vibrations of β-cyclodextrin. The peak observed at 1561 cm^{-1} may be assigned to the bending vibrations of water molecules trapped into the ZrO_2 nano particles

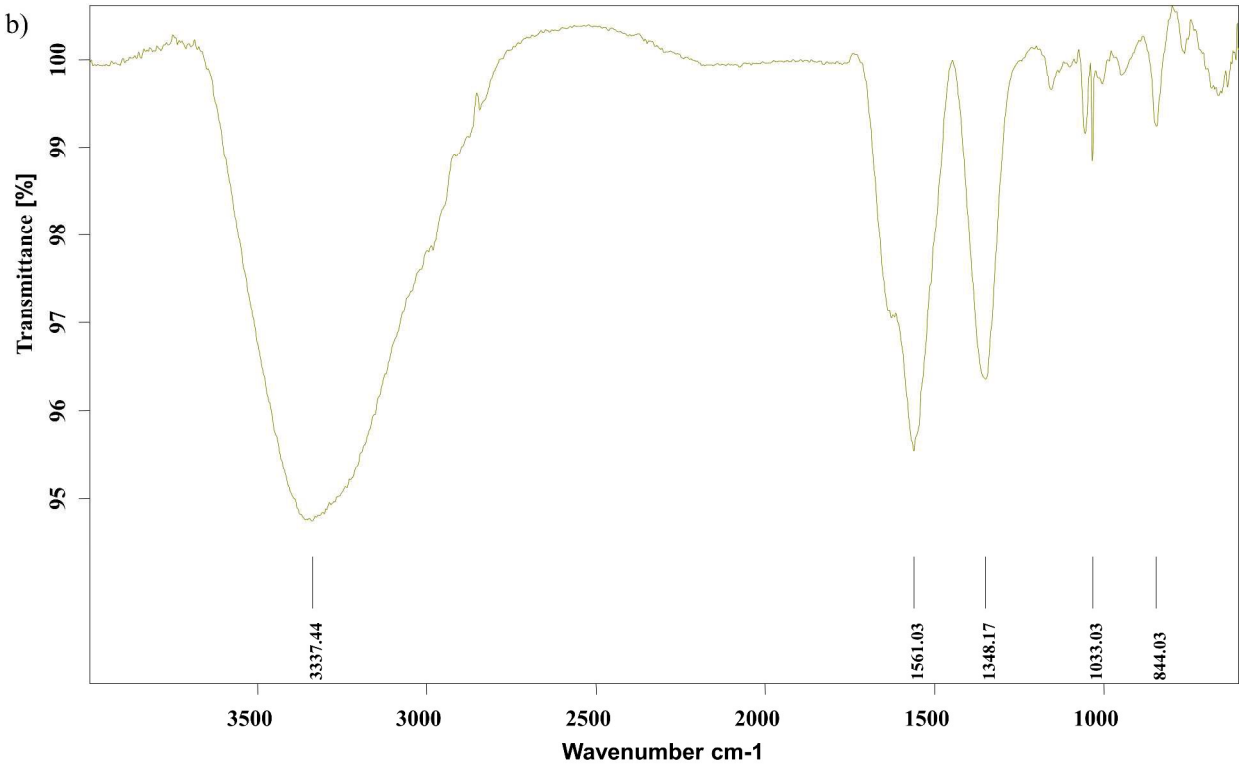
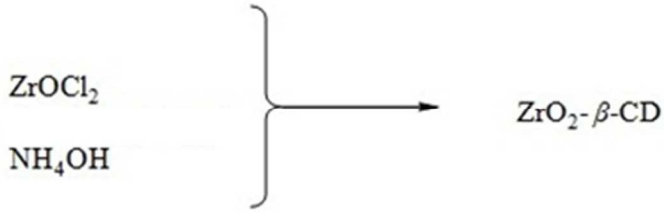


Fig. 1 ATR-IR spectrum of the ZrO_2- supported -β-cyclodextrin



Scheme 2: Preparation of ZrO_2-β-CD nanoparticles

The XRD analysis of ZrO_2 and ZrO_2 supported -β-cyclodextrin nanoparticles indicate five characteristic peaks at 2θ = 30.2°, 35.15°, 50.44°, 60.14°, and 62.98° corresponding to (111), (200), (220), (311), and (331) planes, respectively as shown in Fig.2. All diffraction peaks and positions match with those from the JCPDS card (Joint Committee on Powder Diffraction Standards no. 37-1484) calculated from the Scherer's equation.

$$d = \frac{0.9\lambda}{\beta \cos\theta}$$

where d is the average grain size of the crystallites, λ the incident wavelength, θ, the Bragg angle and β the diffracted full-width at half-maximum (FWHM) in radians caused by the crystallites. The values obtained using the above equation for the ZrO_2 and ZrO_2 supported -β-cyclodextrin nanoparticles were 20 and 1.20 nm, respectively. This reveals that the ZrO_2-β-CD nanoparticles are evenly distributed throughout the specimen, which assists in reducing the size of the nanoparticles.

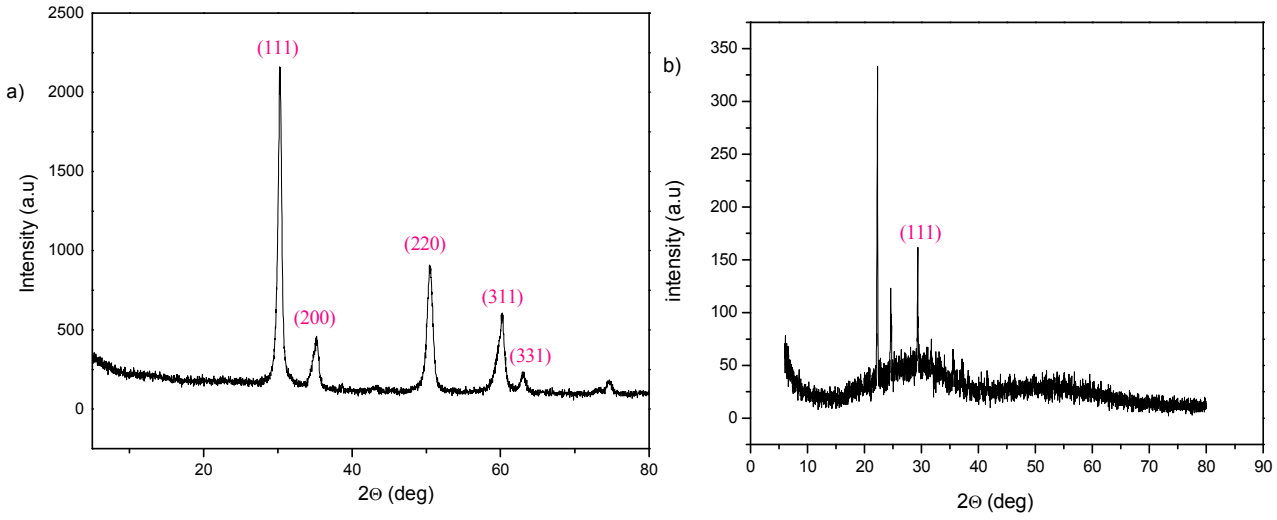


Fig. 2 (a) XRD pattern of the ZrO_2; (b) XRD pattern of the ZrO_2- supported -β-cyclodextrin

The SEM and TEM of the prepared ZrO_2-β-CD nanoparticles were shown in Fig. 3. The TEM image of the catalyst shows that nano particles are highly aggregated. The average size of these particles is about 1-2 nm, which shows a close agreement with the values calculated by XRD data. The SEM image of the supported catalyst confirms that these nanoparticles are uneven-sized particles due to deposition of β-cyclodextrin complex nanoparticles on the surface of ZrO_2 and most of them are almost spherical in shape.

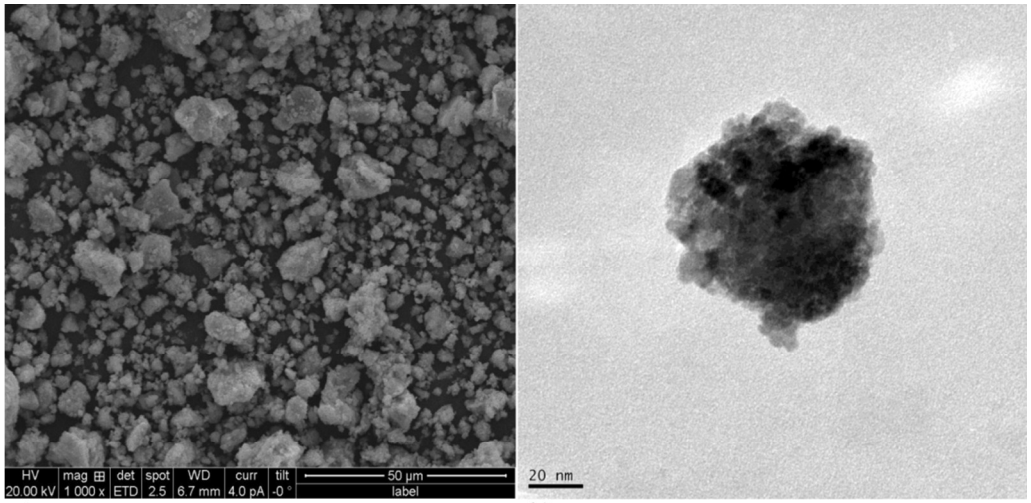


Fig. 3 (a) SEM image of ZrO_2 supported -β-cyclodextrin; (b) TEM image of ZrO_2 supported -β-cyclodextrin.

The At % peaks of the elements were found to be C (39.15 %), O (25.04%) and Zr (35.81%) in the EDAX spectrum of ZrO_2-β-CD nanoparticles as shown in Fig.4.

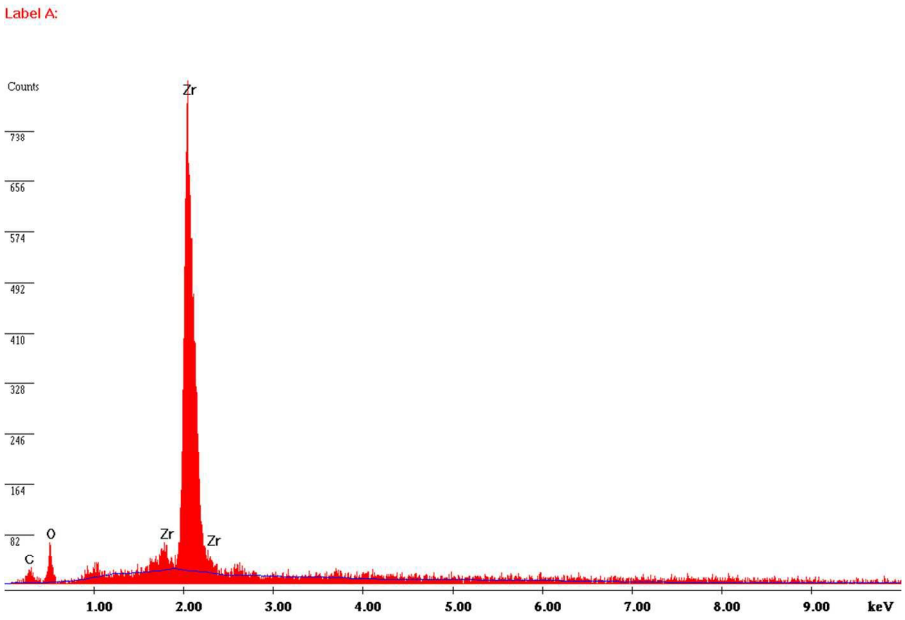
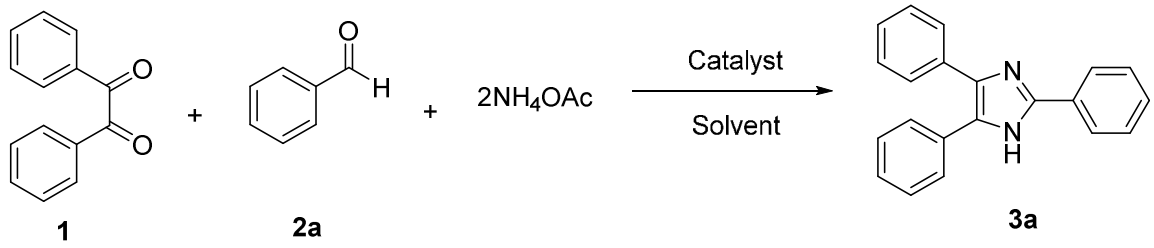


Fig. 4 EDAX spectrum of ZrO_2 supported -β-cyclodextrin.

To optimize the reaction conditions for the synthesis of 2,4,5-trisubstituted imidazoles, benzaldehyde, benzil and ammonium acetate were used as model substrates and the reaction was screened in different solvents, temperatures, and various amounts of catalyst and the results are summarized in Table 1. In the presence of β-CD and water as solvent at 80 ºC, reaction yielded the desired product **3a** in 30% yield (Table 1, entry 1), the low yield may be due to the partial missicibility of benzil and aldehyde in aqueous solvent at 80 °C. Next, a series of catalysts were examined, among them ZrO_2-β-CD was found to be better catalyst for the formation of **3a** with 65% yield in presence of water as solvent at 100 ºC (Table 1, entry 5). We next examined the reaction in presence of various solvents and solvent free conditions (Table 1, entries 6-16). In the presence of solvents the reaction produced the product 3a in low yields (Table 1 entries 1-8) and under solvent free condition the reaction underwent smoothly and gave the desired product in good yield (Table 1 entries 9-15). Initially 20 mol% ZrO_2-β-CD at 100 ºC, gave the desired

product in very low yield (Table 1, entry 11). When the catalyst load was increased from 20 to 40 mol %, it resulted in increase in yield of 3a up to 96% and the reaction was completed in just 40 minutes at 100 ºC (Table 1, entry 13).

Table 1: Condensation of benzil, benzaldehyde, and ammonium acetate using different catalysts and solvents



1 2a 3a

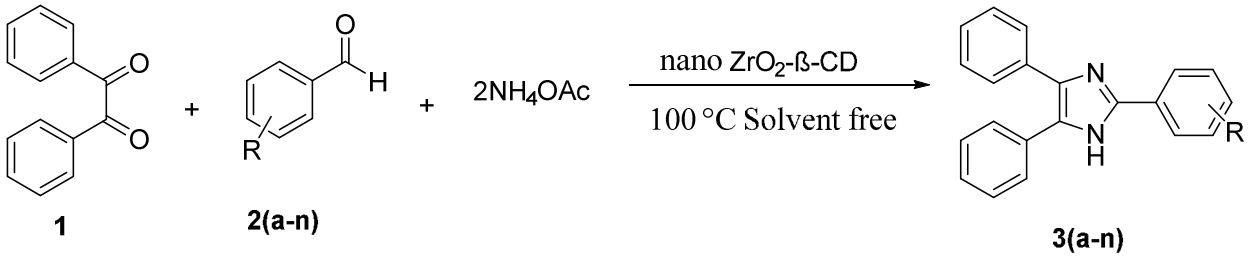
Entry	Catalyst	Catalyst loading (mol %)	Nitrogen source	solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	β-CD	40	NH_4OAc	water	80	7	30
2	ZrO_2-Cu_2(II)-β-CD	40	NH_4OAc	Water	80	6	40
3	ZrO_2-Al_2O_3	40	NH_4OAc	water	100	6	60
4	ZrO_2-β-CD	10	NH_4OAc	Water	100	6	50
5	ZrO_2-β-CD	20	NH_4OAc	Water	100	4	65
6	ZrO_2-Cu_2(II)-β-CD	40	NH_4OAc	DMF	100	8	55
7	ZrO_2-β-CD	40	NH_4OAc	DMF	100	4	60
8	ZrO_2-β-CD	40	NH_4OAc	EtOH	100	3	60
9	β-CD	40	NH_4OAc	Neat	100	2	40
10	ZrO_2-Al_2O_3	40	NH_4OAc	Neat	100	1	50
11	ZrO_2-β-CD	20	NH_4OAc	Neat	100	1.3	50
12	ZrO_2-Cu_2-β-CD	20	NH_4OAc	Neat	100	4	70
13	**ZrO_2-β-CD**	**40**	NH_4OAc	Neat	**100**	**0.4**	**96**
14	ZrO_2-Cu_2(II)-β-CD	40	NH_4OAc	Neat	100	4	70
15	ZrO_2-Al_2O_3	40	NH_4OAc	Neat	100	0.5	60
16	ZrO_2-β-CD	40	NH_4Cl	Neat	100	3	----

[a] Reaction conditions: benzil (1.0 mmol), benzaldehyde (1.0 mmol), NH_4OAc (2.0 mmol), catalyst and solvent (10 mL), or neat. [b] Isolated yield.

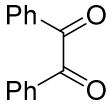
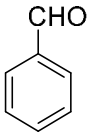
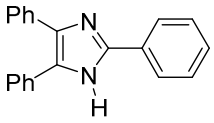
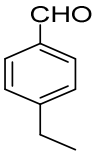
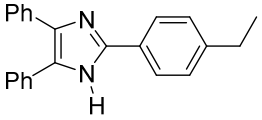
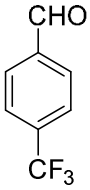
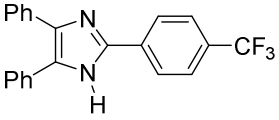
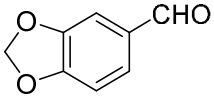
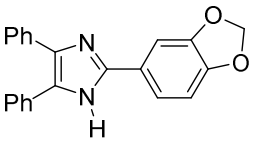
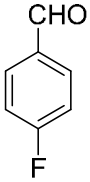
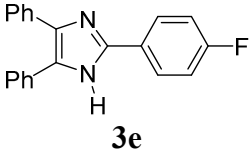
With the optimized reaction condition in hand, we next explored the generality and scope of the protocol using various aldehydes and keeping 1,2-diketone same for the synthesis of 2,4,5-trisubstituted imidazoles. The results are shown in Tables 2. These results show that the reactions are equally facile with both electron-donating and electron-withdrawing substituent's present on

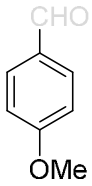
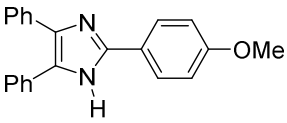
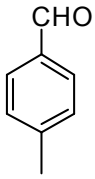
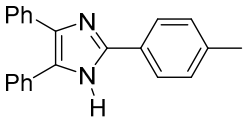
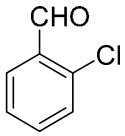
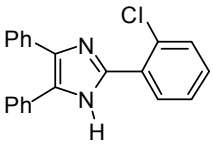
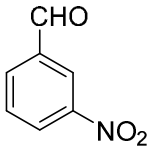
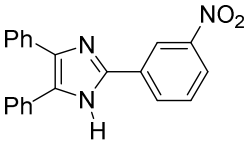
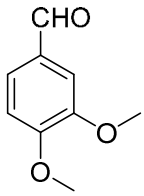
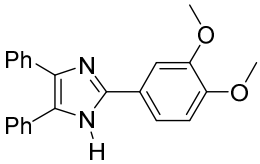
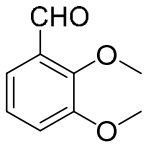
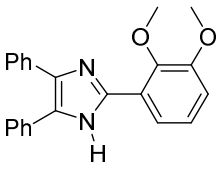
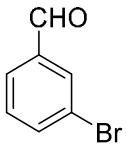
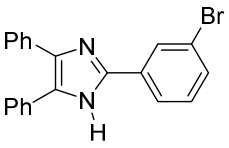
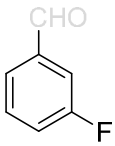
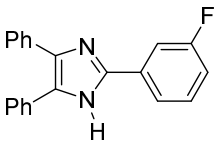
the aromatic aldehydes resulting in high yields of the desired imidazoles. The known products were characterized by comparing their physical properties with those reported in the literature.

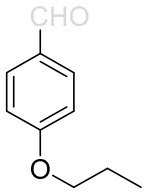
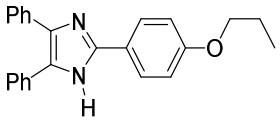
Table 2 : Solvent free synthesis of 2,4,5-trisubstituted imidazoles catalyzed by ZrO_2-β-CD



1 **2(a-n)** **3(a-n)**

Entry	Diketone	R	Product	Time(h)	Yield[b,c](%)
1	 **1**	 **2a**	 **3a**	0.40	96[57]
2	**1**	 **2b**	 **3b**	0.40	85[57]
3	**1**	 **2c**	 **3c**	0.50	86[58]
4	**1**	 **2d**	 **3d**	0.50	87[58]
5	**1**	 **2e**	 **3e**	0.50	89[58]

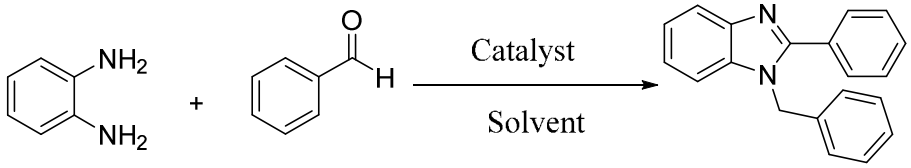
6	**1**	 **2f**	 **3f**	0.35	92[58]
7	**1**	 **2g**	 **3g**	0.45	90[58]
8	**1**	 **2h**	 **3h**	0.50	97[58]
9	**1**	 **2i**	 **3i**	0.45	89[58]
10	**1**	 **2j**	 **3j**	0.35	97[59]
11	**1**	 **2k**	 **3k**	0.35	96
12	**1**	 **2l**	 **3l**	0.40	80[60]
13	**1**			0.45	94

		2m	3m		
14	**1**			0.55	98
		2n	**3n**		

[a] Reaction conditions: 1,2-diketone (1.0 mmol), aldehyde (1.0 mmol), NH_4OAc (2.0 mmol), ZrO_2-β-CD (40 mol %), neat. [b] Isolated yield.[C] Literature reported compounds.

We next explored the generality of this protocol for the synthesis of 1,2-disubstitited benzimidazoles. Initially, benzaldehyde and 1,2-phenylenediamine were selected as model substrates for the synthesis of 1,2-disubstituted benzimidazoles and the results are presented in Table 3. The reaction in presence of ZrO_2-β-CD in EtOH as solvent at room temperature gave desired 1-benzyl-2-phenyl-1*H*-benzo[d]imidazole 5a in 55% yield (Table 3, entry 1). We next examined the reaction using different catalysts such as ZrO_2-β-CD, Nano TiO_2, Nano CuO, Mo/ZrO_2, $ZnO\text{-}Al_2O_3$, β-CD, $ZrO_2\text{-}Al_2O_3$ and $ZrO_2\text{-}Cu_2$-β-CD (Table 3, entries 1-11). Among them ZrO_2-β-CD was found to be better catalyst for the synthesis of 1,2-disubstituted benzimidazoles. We next converged our interest to study the effect of solvents on the product yield. Among various solvent screened, DMF was found to be better and gave the desired product 5a in 85% yield at 100°C (Table 3, entry 4). Then the reaction was performed using ZrO_2-β-CD as catalyst by varying temperature and mol% of catalyst under solvent free condition. Initially 20 mol% of ZrO_2-β-CD at 100 ºC gave only 85% of yield even after 1.3h (Table 3, **entry 13**). Then the reaction was screened by increase in catalyst load from 20 to 40 mol % which gave increase in yield up to 95% (Table 3, **entry 14**).

Table 3: Condensation of benzil, benzaldehyde, and ammonium acetate using different catalysts and solvents



4 **2a** **5a**

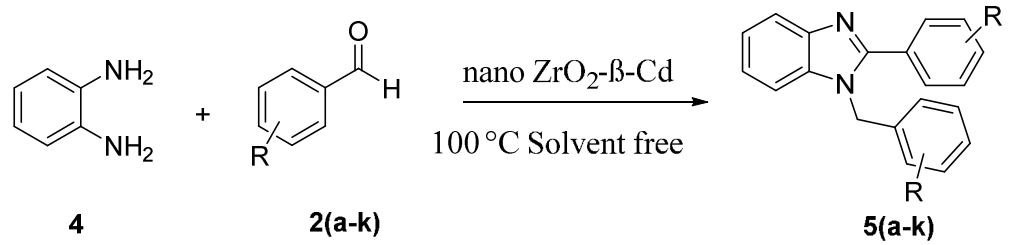
Entry	Catalyst	Mol (%)	Solvent	Temp(ºC)	Time (h)	yield[b]
1	ZrO_2-β-CD	40	EtOH	Rt	12	55
2	ZrO_2-β-CD	40	H_2O	Rt	18	60
3	ZrO_2-β-CD	40	EtOH	100	2	70
4	ZrO_2-β-CD	40	DMF	100	3	85
5	Nano TiO_2	40	DMF	100	8	55
6	Nano CuO	40	DMF	100	12	45
7	Mo/ZrO_2	40	DMF	100	18	60
8	ZnO-Al_2O_3	40	DMF	100	5	50
9	β-CD	40	DMF	100	12	70
10	ZrO_2-Al_2O_3	40	DMF	100	8	60
11	ZrO_2-Cu_2-β-CD	40	DMF	100	5	80
12	ZrO_2-β-CD	10	neat	100	2.3	70
13	ZrO_2-β-CD	20	neat	100	1.3	85
14	**ZrO_2-β-CD**	**40**	**neat**	**100**	**1**	**95**
15	Nano TiO_2	40	neat	100	1.15	75
16	Nano CuO	40	neat	100	2.15	40
17	β-CD	40	neat	100	1.3	60
18	ZnO-Al_2O_3	40	neat	100	2	50

[a] Reaction conditions: 1,2-phenylenediamine (1.0 mmol), benzaldehyde (2.0 mmol), catalyst and solvent (10 mL), or neat. [b] Isolated yield, rt = room temperature

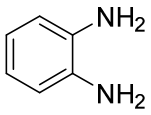
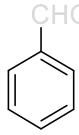
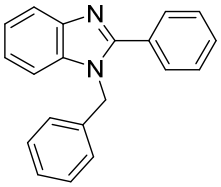
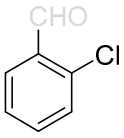
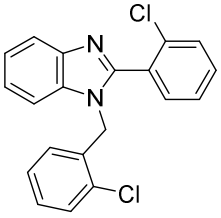
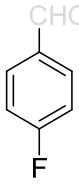
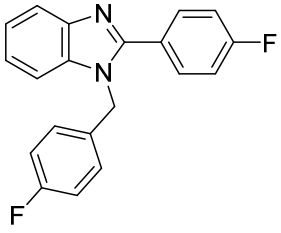
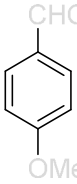
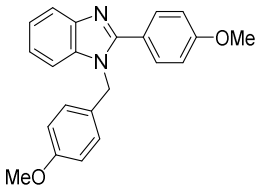
After optimization of the reaction condition, different aldehydes and 1,2-phenylenediamine were used as substrates for the synthesis 1,2-disubstituted benzimidazoles, and the results are shown in Tables 4. Reaction underwent comparatively fast when electron-donating substituent's such as methyl, methoxy, ethyl, or propyl group were present on the substrates. Whereas, the electron-withdrawing substituent's such as CF_3, F, Br, Cl, NO_2 took more time for completion of reaction. Structures of the newly synthesized compounds were characterized by spectroscopic and

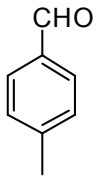
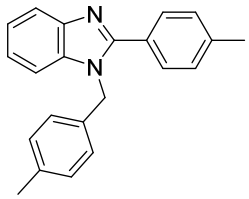
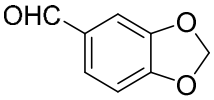
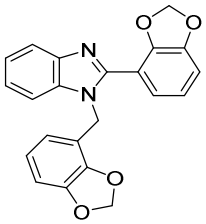
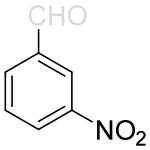
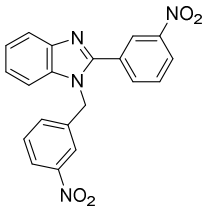
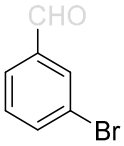
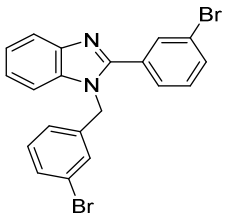
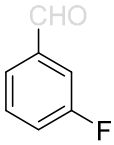
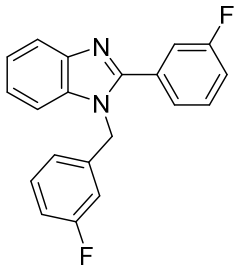
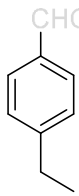
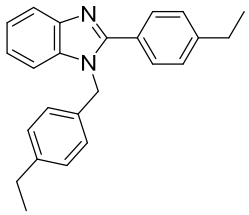
elemental analysis data. The known products were characterized by comparing their physical properties with those reported in the literature.

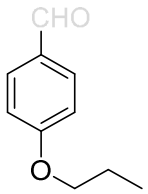
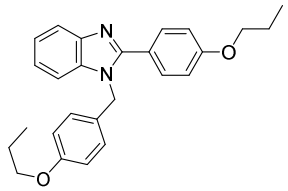
Table 4: Solvent free synthesis of 1,2-disubstituted benzimidazoles catalyzed by ZrO_2-β-CD



4 **2(a-k)** **5(a-k)**

Entry	Diamine	Aldehyde	Product	Time (h)	Yield [b,c](%)
15	 **4**	 **2a**	 **5a**	1.00	93[14]
16	**4**	 **2f**	 **5b**	1.00	85[14]
17	**4**	 **2c**	 **5c**	1.50	95[15]
18	**4**	 **2d**	 **5d**	1.30	87[16]

19	**4**	 **2e**	 **5e**	1.45	92[16]
20	**4**	 **2b**	 **5f**	1.30	96[17]
21	**4**	 **2g**	 **5g**	2.00	80[18]
22	**4**	 **2h**	 **5h**	1.40	93[19]
23	**4**	 **2i**	 **5i**	1.45	88
24	**4**	 **2j**	 **5j**	1.40	90

25	**4**	 **2k**	 **5k**	1.35	90

[a] Reaction conditions: and 1,2-phenylenediamine (1.0 mmol), aldehyde (2.0 mmol), ZrO_2-β-CD (40 mol %) neat. [b] Isolated yield. [c]Literature reported compounds.

Since many nitrogen containing heterocyclic derivatives[61] possess wide range of biological activities we have screened all the synthesized derivatives for their antibacterial activity. The antibacterial activity of the synthesized test samples **3(a-n) and 5(a-k)** were screened for their antibacterial activity against both Gram-positive and Gram-negative bacterial strains, using previous reported procedure.[62] The results shown in Table 5 indicates that these compounds exhibit a variable zone of inhibition ranging from 4-32 mm. These compounds shown moderate antibacterial activity against gram-positive bacteria *Bacillus subtilis (MTCC 121),* with inhibition zone around <19 mm except for the compounds 3b, 3c, 3n, 5a, 5c, 5e-j, which do not show any antibacterial activity. In contrast compounds 3a-3n, 5a-5c and 5g- 5j did not inhibit the growth of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter aeruginosa, Shigella flexneri* (except compounds 3f, 3g, 3h in *Pseudomonas aeruginosa*) even at maximum concentration of 10 µg per disc. However the compound **5f** showed very good inhibition to the growth of *Klebsiella pneumonia* and *Enterobacter aeruginosa* with inhibition value of 32 and 26 mm respectively.

Table 5 Antimicrobial activity of of the synthesized compounds **3(a-n) and 5(a-k).**

Comp	R	Zone of inhibition[a] (mm), dose (5 µg, 10 µg per disc) µg per disc	K.p[b]	B.s[c]	P.a[d]	E.a[e]	S.f[f]	S.t[g]
3a	C_6H_5	5	-	5	-	-	-	5
		10	-	13	-	-	-	10
3b	4-EtC_6H_4	5	-	-	-	-	-	-
		10	-	-	-	-	-	-
3c	4-$CF_3C_6H_4$	5	-	-	-	-	-	-
		10	-	-	10	-	-	-
3d	$C_7H_5O_2$	5	-	5	-	-	-	-
		10	-	13	-	-	-	-
3e	4-FC_6H_4	5	-	8	-	-	-	-
		10	-	18	-	-	-	10
3f	4-OMeC_6H_4	5	-	9	5	-	-	-
		10	-	18	12	-	-	-
3g	4-MeC_6H_4	5	-	9	6	-	-	-
		10	-	18	13	-	-	-
3h	2-ClC_6H_4	5	-	8	6	-	-	-
		10	-	19	15	-	-	-
3i	3-$NO_2C_6H_4$	5	-	7	-	-	-	-
		10	8	15	-	-	-	-
3j	3,4-di$OMeC_6H_3$	5	-	8	-	-	-	-
		10	-	17	-	-	-	-
3k	2,3-di$OMeC_6H_3$	5	-	5	-	-	-	-
		10	-	13	-	-	-	-
3l	3-BrC_6H_4	5	-	5	-	-	-	-
		10	-	11	-	-		-
3m	3-FC_6H_4	5	-	6	-	-	-	-
		10	-	13	-	-	-	10
3n	4-PropC_6H_4	5	-	-	10	-	-	-
		10	-	-	-	-	-	-
5a	C_6H_5	5	-	-	-	-	5	-
		10	-	-	-	-	12	18
5b	2-ClC_6H_4	5	-	7	-	-	8	7
		10	-	14	20	-	13	15
5c	4-FC_6H_4	5	-	-	-	-	4	7
		10	-	-	-	-	12	15
5d	4-OMeC_6H_4	5	10	-	-	13	7	6
		10	15	10	-	26	10	14
5e	4-MeC_6H_4	5	8	-	-	14	6	5
		10	13	-	-	**26**	10	11
5f	$C_7H_5O_2$	5	15	-	-	13	7	4
		10	**32**	-	-	**26**	12	13
5g	3-$NO_2C_6H_4$	5	-	-	-	-	-	8
		10	-	-	17	-	9	16

5h	3-BrC_6H_4	5	-	-	-	-	-	-
		10	-	-	-	-	-	-
5i	3-FC_6H_4	5	-	-	-	-	-	-
		10	-	-	-	-	-	-
5j	4-EtC_6H_4	5	-	8	-	-	8	-
		10	-	15	-	-	16	13
5k	4-$PropC_6H_4$	5	5	--	-	-	5	-
		10	10	--	-	-	12	9
Streptomycin		10	**22**	24	**23**	18	20	17

[a]The values indicate the average diameters in mm (of two trials) for the zone of growth inhibition observed after 24 h of incubation at 37 °C. [b]*Klebsiella pneumoniae MTCC 7407*; [c]*Bacillus subtilis MTCC 121*; [d]*Pseudomonas aeruginosa - MTCC 7903*; [e]*Enterobacter aeruginosa MTCC 7325*; [f]*Shigella flexneri MTCC 1457*; [g]*Salmonella typhi MTCC 733.*

Conclusion

In conclusion, we have developed an efficient and safe protocols for the synthesis of 2,4,5-trisubstituted imidazoles and 1,2-disubstituted benzimidazoles under solvent free conditions. More efficient nanoparticle-catalyst ZrO_2 supported -β-cyclodextrin (1–5 nm range) was easily prepared by co-precipitation method. The analysis data reveal that the nano ZrO_2 supported -β-cyclodextrin was an effective heterogeneous reusable catalyst for the synthesis of 2,4,5-trisubstituted imidazoles and 1,2-disubstituted benzimidazoles under solvent-free mild conditions. Further the compounds have been screened for the antibacterial activity. Compound **5f** at 10µg per disc showed potent inhibitory activity against *K.pneumoniae,* compared to the standard (Streptomycin 10µg per disc) at the same concentration. None the less, further studies needed to be conducted for molecular mechanism of **5f** derivatives against the human pathogen *K.pneumonia.* The present study revealed the potential application and development of synthetic novel molecules against human pathogen and it also proposed for some more studies relating to antimicrobial during further studies.

Experimental Section

General Methods

Zirconium oxychloride ($ZrOCl_2.8H_2O$, >99.0%), ammonia ($NH_3.H2O$, 25%) was purchased from s.d. Fine-Chem Ltd., India. β-cyclodextrin was purchased from Sigma-Aldrich India. Deionized water was used for all workup procedures. Melting points were measured on secor INDIA apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on VNMRS-400 (Agilent Technologies) NMR spectrometer in $CDCl_3$. Tetramethylsilane (TMS; δ = 0.00 ppm) served as internal standard. The corresponding residual non-deuterated solvent signal ($CDCl_3$: δ = 77.00 ppm) was used as internal standard for ^{13}C NMR. Performed column chromatography on silica gel 60-120 mesh (Merck). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Mass spectra were measured with Micromass Q-Tof (HRESI-MS). DMF was dried over CaH_2 for 2 h and filtered. The catalyst was characterized by ATR-Fourier transform infrared (ATR-IR) spectra, recorded using a Thermo-Nicolet FTIR spectrometer (Model 5700, Madison, WI) fitted with a single bounce attenuated total reflectance (ATR) accessory with a ZnSe crystal of range 400-4000 cm^{-1}. X-ray powder diffraction (PXRD) was carried out on a XRD 7000, Shimandzu diffractometer with CuK_α radiation. Scanning electron microscopy (SEM) images were obtained using a JEOL JXA-8530F microscope. Transmission electron microscopy (TEM) images were performed on PHILIPS CM200 electron microscope at an acceleration voltage of 20-200kV. TGA thermograms of the nanoparticles were obtained under nitrogen on a Perkin–Elmer TGA 7 analyzer at a heating rate of 20°C min^{-1}.

Preparation of ZrO_2-supported -β-cyclodextrin nanoparticles

The ZrO_2-supported -β-cyclodextrin nanoparticles were prepared by a chemical co-precipitation method.[25] 2.42 g of zirconium oxychloride ($ZrOCl_2.8H_2O$) and 1.04 g of -β-cyclodextrin were dissolved in 50 mL of deionized water under intense stirring at 90°C. Subsequently, ammonia (25%) was added drop wise to the reaction mixture with stirring. The nanoparticles formed were collected by filtration, washed with distilled water repeatedly, and dried for 24 h at room temperature in a high vacuum.

General procedure for the synthesis of 2,4,5-trisubstituted imidazole derivatives or 2,5-disubstituted benzimidazole derivatives in the presence of ZrO_2 supported -β-cyclodextrin nanoparticles as catalyst under solvent free conditions.

To a mixture, of benzil (1 mmol), benzaldehyde (1 mmol), and NH_4OAc (2 mmol) for 2,4,5-trisubstituted imidazole derivatives or to a mixture of *o*-phenylenediamine (1 mmol) and aldehyde (2 mmol) for 1,2-disubsubstituted benzimidazole derivatives, was added ZrO_2-β-Cd (40 mol %). The resulting mixture was heated at 100 $^{\circ}$C on an oil bath under neat conditions for appropriate time till the completion of the reaction. After completion of reaction, as monitored by TLC (eluent: petroleum ether: ethyl acetate: 7:3), the reaction was cooled to room temperature. The solid thus formed was dissolved in acetone and the catalyst separated by filtration. The mixture was concentrated on a rotary evaporator under reduced pressure and the product obtained was washed with water and recrystallized from acetone–water 9 : 1 (v/v) to offer the pure 2,4,5-trisubstituted imidazole derivatives.

Reusability studies

Recovery of the nano- ZrO_2 supported -β-cyclodextrin catalyst was easy and efficient. When the reaction was complete, the precipitated products were dissolved by acetone and nano- ZrO_2

supported -β-cyclodextrin was separated by centrifugation followed by decantation (ethanol, 5 ml). The isolated solid phase (nano- ZrO_2 supported -β-cyclodextrin) was then dried under reduced pressure and reused for four runs without any appreciable loss in the product yield and its catalytic activity. The same results were obtained for the catalyst recovery in condensation of o-phenylenediamine (1mmol) and benzaldehyde (2 mmol) for synthesis of the corresponding 1,2-disubstituted benzimidazole under solvent-free conditions. Therefore, the methodologies are environmentally friendly, cost effective and industrially important because of the catalyst reuse and the use of safe reaction media.

Acknowledgements

YRG is thankful to UGC-BSR for meritorious fellowship Order no. DV-5/662/RFSMS/2012–13, New Delhi, India for financial support and we are also thankful to IOE, University of Mysore and NCBS, Bengaluru, Karnataka, India for their support in carrying out research work regarding the single crystal XRD and TEM analysis.

References:

1. (a) C. Guo, C. Zhang, X. Li, W. Li, Z. Xu, L. Bao, Y. Ding, L. Wang, S. Li, *Bioorganic & Medicinal Chemistry Letters*., 2013, **23**, 5850-5854; (b) S. Hack, B. Wörlein, G. Höfner, J. Pabel , K. T. Wanner, *European Journal of Medicinal Chemistry*., 2011, **46**, 1483-1498; (c) J. G. Lombardino, E. H. Wiseman, *Journal of Medicinal Chemistry*., 1974, **17**,1182-1188; (d) X. Q. Wang, L. X. Liu, Y. Li, C. J. Sun, W. Chen, L. Li, H. B. Zhang, X. D. Yang, *European Journal of Medicinal Chemistry*., 2013, **62**, 111-121; (e) M. Mccann, R. Curran, M. Ben-Shoshan, V. McKee, M. Devereux, K. Kavanagh, A. Kellett, *Polyhedron*., 2013, **56**, 180–188; (f) H . Nabata, M. Uchino, A. Okazaki, T.Yamazaki, K. Sakai, *Japan. J. Pharmacol*., 1987, **44**, 93-96; (g) J. Liu, J .Qiu, M .Wang, L .Wang, L. Su, J .Gao, Q .Gu, J .Xu, S. L Huang, L. Q. Gu, Z. S. Huang, D. Li, *Biochimica et Biophysica Acta*., 2014, **1840**, 2886–2903;(h) J .Kang, L .Han, Z. Chen, J .Shen, J .Nan, Y .Zhang, *Food Chemistry*., 2014, **159**, 445–450.
2. J. Kulhánek, F .Bureš, *Beilstein J. Org. Chem*., 2012, **8**, 25–49.
3. C .Yao-Te, H .So-Lin, C .Guan-Yu, S .Ming-Hsin, A. S .Thounaojam, D .Eric Wei-Guang, and W. Kung-Hwa, *Adv. Funct. Mater*., 2008, **18**, 2356–2365.
4. W .Zhiming, L .Ping, C .Shuming, G .Zhao, S .Fangzhong, Z .Wensi, X .Yuanxiang, K. W. Hoi Sing and M. Yuguang . *J.Mater. Chem*., 2011, **21**, 5451–5456.
5. Y. Zijun and R. B. Elliot *J. Phys. Chem. A*.; 2013, **117**, 1756−1764.

6. B. Milde, D. Schaarschmidt, T .Rüffer, H .Lang, *Dalton Trans*., 2012, **41**, 5377-5390.
7. W. A. Denny, G. W. Rewcastle and B. C. Baguley, *J. Med. Chem*., 1990, **33**, 814.
8. T. Fonseca, B. Gigante and T. L. Gilchrist, *Tetrahedron.*, 2001, **57**, 1793.
9. R.-H. Tan, L.-C. Ding and X.-J. Wei, Chin. *J. Med. Chem*., 2001, **11**, 259.
10. D. Yang, D. Fokas, J. Li, L. Yu and C. M. Baldino, *Synthesis*, 2005, **47**.
11. Bai, Y.; Lu, J.; Shi, Z.; Yang, B. *Synlett* 2001, **11**, 544–546.
12. Hasegawa, E.; Yoneoka, A.; Suzuki, K.; Kato, T.; Kitazume, T.; Yangi, K. *Tetrahedron* 1999, **55**, 12957–12968.
13. G. A. Molander, K . Ajayi, *Org. Lett*., 2012, **14**, 4242–4245.
14. G. Pranab, M. Amitava, *Tetrahedron Lett*., 2012, **53**, 6483–6488.
15. S. Samuthirarajan, K. Mayilvasagam, *Tetrahedron Lett*., 2014, **55**, 1971–1974.
16. R. Chebolu , D. N. Kommi, D. Kumar, N. Bollineni, A. K. Chakraborti, *J. Org. Chem.,* 2012, **77** , 10158–10167
17. D. Kumar, D. N. Kommi, R. Chebolu, S. K. Garg, R. Kumar, A. K. Chakraborti, *RSC Adv.,* 2013**, 3**, 91-98.
18. M. Chakrabarty, R. Mukherjee, S. Karmakar, and Y. Harigaya, Monatshefte fu¨ r Chemie 2007, **138**, 1279–1282.
19. S. Radheshyam, S. Sachin , N. Jayashree , *Tetrahedron Lett.;* 2013, **54**, 6986–6990.
20. Vikash Kumar, G. K. Dipratn, C. Amrita, B. Mainak, *Tetrahedron Lett*., 2013, **54**, 5505–5509.
21. M. I. Suleman, K. M. Vinod, K. M. Sisir, *Tetrahedron Lett*., 2013, **54**, 579–583.
22. (a) H. Debus, *Ann. Chem. Pharm*., 1858, **107**, 199–208;
23. (a) K .Sivakumar, A .Kathirvel, A .Lalitha. *Tetrahedron Lett*., 2010, 51, 3018–3021.;(b) S .Narayana Murthy, B .Madhav, Y. V. D. Nageswar. *Tetrahedron Lett*., 2010, **51**, 5252–5257; (c) I. M. David, M . Bahramnejad, M. Dabiri. *Tetrahedron Lett*. 2013, **54**, 2591–2594 (d) S .Maity, S. Pathak, A .Pramanik. *Tetrahedron Lett*., 2013, **54**, 2528–2532.; (e) N.P. Amit, K. A. Devendra, *Tetrahedron Lett*., 2014, **55**, 1835–1838; (f) Z . Zohre and S. Javad, *New J. Chem*., 2014, **38**, 4555-4565; (g) S .Javad, A .Zahra, N .Simin. DOI: 10.1016/j.jscs.2012.10.012. (h) P. F. Zhang and Z. C. Z. Chen, S*ynthesis*, 2001, 2075–2077.
24. S. Tan, X. Li, Y. Guo, Z. Zhang, *Nanoscale*. **2013**, **5**, 860-872.
25. T. Yong, I. Roy, M. T. Swihart, P. N. Prasad, *J. Mater. Chem*. 2009, **19**, 4655-4672.
26. Z. Zarnegar and J. Safari, *New J. Chem.,* 2014, **38**, 4555-4565.
27. (a) L. Bao-Le, Z.Mo, H. Hai-Chuan, D. Xia and Z. Zhan-Hui, *New J. Chem.,* 2014, **38**, 2435; (b) D. A. Kotadia, U. H. Patel, S. Gandhi and S. S. Soni, *RSC Adv*., 2014,**4**, 32826-32833.
28. (a) Y. Ding, Y. Wang, L. Zhang, H. Zhang, C. M. Li, Y. Lei, *Nanoscale.,* 2011, **3**, 1149-1157; (b) O. A. Sadik, A. L. Zhou, S. Kikandi, N. Du, Q. Wang, K. Varner, *J. Environ. Monit.*, 2009, **11**, 1782-1800; (c) X. D. Wang, O. S. Wolfbeis, J. Robert, Meier*, Chem. Soc. Rev*., 2013, **42**, 7834-7869.
29. D. Jariwala, V. K. Sangwan, L. J. Lauhon, T. J. Marks, M. C. Hersam, *Chem. Soc. Rev.,* 2013, **42**, 2824-2860.
30. J. Liao, Z. Yang, H. Wu, D. Yan, J. Qiu, Z. Song, Y. Yang, D. Zhou and Z. YinH. Kang, Y. Zhu, X. Yang, J. Shen, C. Chen, C. Li, *J. Mater. Chem. C.,* 2013, **1**, 6541–6546.
31. H. Kang, Y. Zhu, X. Yang, J. Shen, C. Chen, C. Li, *New J. Chem.*, 2010, **34**, 2166.
32. R. Narayanan, M. A. El-Sayed, *J. Phys. Chem. B.,* 2005, **109**, 12663-12676.

33. (a) J. Zhang, P. X. Ma, *Advanced Drug Delivery Reviews.,* 2013, **65**, 1215-1233. (b) C. Tudisco,V. Oliveri, M. Cantarella, G. Vecchio, and G. G. Condorelli, *Eur. J. Inorg. Chem*., 2012, 5323–5331.
34. B. Aswathy, G. S. Avadhani, S. Suji, G. Sony, *Front. Mater. Sci.,* 2012, **6**, 168–175.
35. K. Cai, J. Li, Z. Luo, Y. Hu, Y. Hou and X. Ding, *Chem.Commun*., 2011, **47**, 7719–7721.
36. R. Freeman, T. Finder, L. Bahshi, and I. Willner, *Nano Lett.,* 2009, **9**, 2073-2076.
37. (a) B. Madhav, S. Narayana Murthy, V. Prakash Reddy, K. Rama Rao, Y. V. D. Nageswar, *Tetrahedron Lett*.; 2009, **50**, 6025–6028; (b) K. Ramesh, K. Karnakar, G. Satish, B. S. P. Anil Kumar, Y. V. D. Nageswar, *Tetrahedron Lett*., 2012, **53**, 6936–6939; (c) Dipak R. Patil,Yogesh B. Wagh, Pravin G. Ingole,Kripal Singh and Dipak S. Dalal, *New J. Chem*., 2013,**37**, 3261-3266; (d) Babak Kaboudin, Ramin Mostafalu and Tsutomu Yokomatsu, *Green Chem*., 2013, **15**, 2266.
38. K. Tanabe, *Mater. Chem. Phys.* 1985, **13**, 347–364.
39. R. C. Garvie, R. H. Hannink, R. T. Pascoe, *Nature*, 1975, **258**, 703–704.
40. G. D. Wilk, R. M. Wallace, J. M. Anthony, *J. Appl. Phys.,* 2001, **89**, 5243-5275.
41. G. Y. Guo, Y. L. Chen, *J. Mater. Chem.,* 2001, **11**, 1283-1287
42. S. F. Yin, B. Q. Xu, *Chem Phys Chem.* 2003, **4**, 277-281.
43. A. H. Heuer, L. W. Hobbs, Science and technology of zirconia, American Ceramic Society, Columbus and Ohio, 1981, vol. **3**.
44. M. Inoue, H. Kominami, T. Inui, *Appl. Catal. A.* 1993, **97**, L25–L30.
45. J. Joo, T. Yu, Y. W. Kim, H. M. Park, F. Wu, J. Z. Zhang, T. Hyeon, *J. Am. Chem. Soc.* 2003, **125**, 6553–6557.
46. R. C. Buchanan, S. Pope, *J. Electrochem. Soc.* 1983, **130**, 962-966.
47. A. Krell, J. Klimke, T. Hutzler, *Opt. Mater.* 2009, **31**, 1144–1150.
48. J. Robertson, *Rep. Prog. Phys.* 2006, **69**, 327–396.
49. G. Liu and Y. Lin, *Anal. Chem.* 2005, **77**, 5894–5901.
50. S .Liu, and M. Y. Han, *Chem.–Asian J.* 2010, **5**, 36–45.
51. J. Lu, J. B. Zang, S. X. Shan, H. Huang, Y. H. Wang, *Nano Lett*. 2008, **8**, 4070–4074.
52. T. Z. Sholklapper, V. Radmilovic, C. P. Jacobson, S. J. Isco, L. C. De Jonghe, *Electrochem. Solid-State Lett*. 2007, **10**, B74–B76.
53. X. Luo, A. Morrin, A. J. Killard, M. R. Smyth, *Electroanalysis,* 2006, **18**, 319–326.
54. S. A. Steiner, Th. F. Baumann, B. C. Bayer, R. Blume, M. A. Worsley, W. J. Moberly Chan, E. L. Shaw, R. Schlogl, A. John Hart, S. Hofmann, B. L. Wardle, *J. Am. Chem. Soc*. 2009, **131**, 12144–12154.
55. (a) Y. R. Girish, K. S. S. Kumar, H. S. Manasa and S. Shashikanth, *J. Chin. Chem. Soc.* 2014, **61**, 1175-1179; (b) Y. R. Girish, K. S. S. Kumar, U. Muddegowda, N. K. Lokanath, K. S. Rangappa, S. Shashikanth, *RSC Adv.,* 2014, **4**, 55800–55806; (c) Y. R. Girish, K. R. Raghavendra, D. Nagaraja, K. S. S. Kumar, S. Shashikanth, *Chin. J. Chem.* 2015, **33**, 181-184.
56. L. Bai, A. F. Wyrwalski, C. Machut, P. Roussel, E. Monflier, A. Ponchel, *Cryst Eng Comm.,* 2013, **15**, 2076.
57. K. Ramesh, S. Narayana Murthy, K. Karnakar, Y.V.D. Nageswar, Kukuma Vijayalakhshmi, Bethala L.A. Prabhavathi Devi, R.B.N. Prasad, *Tetrahedron Lett*., 2012, **53**, 1126-1129.
58. X.Min , L. Yue-dong , *Journal of Molecular Catalysis A: Chemical*., 2007, **265** , 205–208.
59. S. Saikat Das, H. Parasa , K. Dilip, *Tetrahedron Lett.,* 2008, **49**, 2216-2220.

60. M. Jafarpour, A. Rezaeifard,M. Ghahramaninezhad and T. Tabibi, *New J. Chem*., 2013, **37**, 2087—2095.
61. (a) V. Srinivas, C. D. Mohan, C. P. Baburajeev, S. Rangappa, S. Jagadish, J. E. Fuchs, A. Y. Sukhorukov, Chandra, D. J. Mason, K. S. Sharath Kumar, M. Madegowda, A. Bender, Basappa, K. S. Rangappa, *Bioorg. Med. Chem. Lett*., 2015, **25**, 2931. (b) K. S. Sharath Kumar, A. Hanumappa, M. Hegde, K. H. Narasimhamurthy, S. C. Raghavan, K. S. Rangappa, *Eur J Med Chem.,* 2014, **81**, 341. (c) K. S. Sharath Kumar, A. Hanumappa, M. Vetrivel, M. Hegde, Y. R. Girish, T. R. Byregowda, S. Rao, S. C. Raghavan, K. S. Rangappa, *Bioorg. Med. Chem. Lett*., 2015, **25**, 3616-3620.
62. P. Bandyopadhya, M. Sathe, S. Ponmariappan, S. Sharma, P. Sharma, A.K. Srivastava, M. P. Kaushik, *Bioorg. Med. Chem. Lett*., 2011, **21**, 7306–7309.

ZrO_2-β-cyclodextrin catalyzed synthesis of 2,4,5-trisubstituted imidazoles and 1,2-disubstituted benzimidazoles under solvent free conditions and evaluation of their antibacterial study